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PATENT

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicant: F. Haviv, et al.

Group Art Unit: 1653

Serial No.: 09/703,233

Examiner: David. Lukton

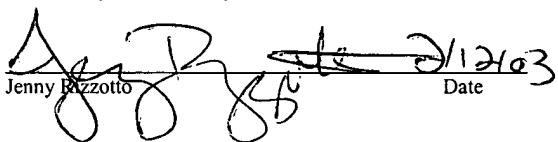
Filed: October 31, 2000

Certificate of Mailing under 37 CFR §1.8(a):
I hereby certify that this paper (along with any paper referred to as being attached or enclosed) is being deposited with the United States Postal Service with sufficient postage as First Class Mail addressed to:

For: N-ALKYLATED PEPTIDES
HAVING ANTIANGIOGENIC
ACTIVITYCommissioner for Patents
Washington, D.C. 20231

Case No.: 6632.US.O2

Date of Deposit: February 12, 2003


Jenny Rizzotto Date 2/12/03TRANSMITTAL LETTER

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The Commissioner for Patents
Washington, D.C. 20231

Dear Sir:

Enclosed herewith for the patent application identified above entitled, N-ALKYLATED PEPTIDES HAVING ANTIANGIOGENIC ACTIVITY, are the following:

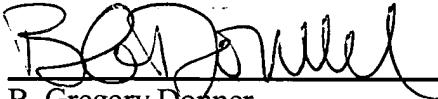
1. Response to Restriction Requirement;
2. Extension of Time (37 CFR 1.136(a)); and
3. Return Receipt Postcard

The Commissioner is hereby authorized to charge any additional Filing Fees required under 37 CFR 1.16, as well as any patent application processing fees under 37 CFR 1.17 associated with this communication for which full payment had not been tendered, to Deposit Account No. 01-0025.



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Respectfully submitted,
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Agent for Applicants



PATENT

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicant: F. Haviv, et al.

Serial No.: 09/703,233

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For: N-ALKYLATED PEPTIDES
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Washington, D.C. 20231

Date of Deposit: February 12, 2003

Jenny Rizzotto 2/12/03
Jenny Rizzotto Date

RESPONSE TO RESTRICTION REQUIREMENT
AND AMENDMENT A

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Director of Patents and Trademarks
Washington, D.C. 20231

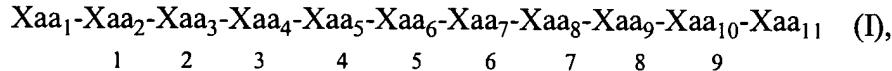
Dear Sir:

This communication is responsive to the Restriction Requirement dated September 30, 2002, having a period of response through February 28, 2003, pursuant to a four (4) month extension of time under 37 C.F.R. §§ 1.136(a).

Kindly enter this amendment and reconsider the application in view of the accompanying remarks.

Please replace claim 1 with the correspondingly numbered claim.

1 (Amended). A compound having a formula:



or a pharmaceutically acceptable salt thereof, wherein

at least one amide bond of an amino acid residue represented by Xaa₃, Xaa₄, Xaa₅,

Xaa₆, Xaa₇, Xaa₈, Xaa₉, and Xaa₁₀ is N-alkylated;

Xaa₁ is absent or Xaa₁ is selected from the group consisting of hydrogen, N-methylprolyl, and an acyl group, wherein the acyl group is selected from the group consisting of

$R^1-(CH_2)_n-C(O)-$, wherein n is an integer from 0 to 8 and R¹ is selected from the group consisting of N-acetylamino, alkoxy, alkyl, aryl, carboxy, cycloalkenyl, cycloalkyl, heterocycle, and hydroxy; and

$R^2-CH_2CH_2-O-(CH_2CH_2O)_p-CH_2-C(O)-$, wherein p is an integer from 1 to 8 and R² is selected from the group consisting of hydrogen, N-acetylamino, and alkyl;

provided that Xaa₁ is absent only when Xaa₂ is N-(R³)-prolyl;

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Xaa₂ is an N-alkylated amino acid selected from the group consisting of N-(R³)-alanyl, N-(R³)-glycyl, N-(R³)-norvalyl, and N-(R³)-prolyl, wherein R³ is C₁-C₅-alkyl; or Xaa₂ is an N-unalkylated amino acid selected from the group consisting of

β -alanyl,
D-alanyl,
4-aminobutyryl,
(1R,3S)-1-aminocyclopentane-3-carbonyl,
(1S,3R)-1-aminocyclopentane-3-carbonyl,
(1R,4S)-1-aminocyclopent-2-ene-4-carbonyl,
(1S,4R)-1-aminocyclopent-2-ene-4-carbonyl,
asparaginyl,
3-(4-chlorophenyl)alanyl,
3-(4-cyanophenyl)alanyl,
glutaminyl,
glutamyl,
glycyl,
4-hydroxyprolyl,
3-(4-methylphenyl)alanyl,
prolyl,
seryl, and
threonyl;

Xaa₃ is an N-alkylated amino acid selected from the group consisting of N-(R³)-alanyl, N-(R³)-glycyl, N-(R³)-leucyl, and N-(R³)-phenylalanyl, wherein R³ is as defined above; or Xaa₃ is an N-unalkylated amino acid selected from the group consisting of

alanyl,
(1S,3R)-1-aminocyclopentane-3-carbonyl,
(1S,4R)-1-aminocyclopent-2-ene-4-carbonyl,
asparaginyl,
aspartyl,
3-(3-cyanophenyl)alanyl,
3-(4-cyanophenyl)alanyl,
glutaminyl,
glycyl,
leucyl,
lysyl(N-epsilon-acetyl),
3-(4-methylphenyl)alanyl,
norvalyl,
proyl, and
phenylalanyl;

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Xaa₄ is an N-alkylated amino acid selected from the group consisting of N-(R³)-alanyl, N-(R³)-glycyl, N-(R³)-homophenylalanyl, N-(R³)-isoleucyl, N-(R³)-leucyl, N-(R³)-norvalyl, N-(R³)-phenylalanyl, N-(R³)-D-phenylalanyl, N-(R³)-seryl, N-(R³)-tyrosyl, N-(R³)-valyl, and N-(R³)-D-valyl, wherein R³ is as defined above; or Xaa₄ is an N-unalkylated amino acid selected from the group consisting of

alanyl,
alloisoleucyl,
allylglycyl,
2-aminobutyryl,
(1R,4S)-aminocyclopent-2-ene-4-carbonyl,
asparaginyl,
aspartyl,
3-[2-(5-bromothienyl)]alanyl,
3-(3-chlorophenyl)alanyl,
3-(4-chlorophenyl)alanyl,
3-(3-cyanophenyl)alanyl,

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cyclohexylalanyl,
3-(3,4-dimethoxyphenyl)alanyl,
3-(3-fluorophenyl)alanyl,
3-(4-fluorophenyl)alanyl,
glutamyl,
glycyl,
histidyl,
homophenylalanyl,
homoseryl,
isoleucyl,
leucyl,
lysyl(N-epsilon-acetyl),
methionyl,
methionyl(sulfone),
3-(4-methylphenyl)alanyl,
3-(naphth-1-yl)alanyl,
3-(naphth-2-yl)alanyl,
norornithyl,
norvalyl,
phenylalanyl,
phenylglycyl,
prolyl,
3-(3-pyridyl)alanyl,
3-(4-thiazolyl)alanyl,
3-(2-thienyl)alanyl,
seryl,
seryl(O-benzyl),
styrylalanyl,
tryptyl,
tyrosyl,
valyl, and
D-valyl;

Xaa₅ is an N-alkylated amino acid selected from the group consisting of N-(R³)-D-homophenylalanyl, N-(R³)-D-isoleucyl, N-(R³)-D-leucyl, and N-(R³)-D-phenylalanyl, wherein R³ is as defined above; or Xaa₅ is an N-unalkylated amino

acid selected from the group consisting of

D-alanyl,
alloisoleucyl,
D-alloisoleucyl,
D-2-aminobutyryl,
D-3-(4-aminophenyl)alanyl,
D-asparaginyl,
D-3-(3-benzothienyl)alanyl,
D-*t*-butylglycyl,
D-(chlorophenyl)alanyl,
D-citrullyl,
D-3-(3-cyanophenyl)alanyl,
D-cyclohexylalanyl,
cyclohexylglycyl,
D-cysteinyl(S-acetamidomethyl),
D-cysteinyl(S-*t*-butyl),
D-3-(3,4-difluorophenyl)alanyl,
D-(3,4-dimethoxyphenyl)alanyl,
D-glutaminyl,
glycyl,
D-homophenylalanyl,
D-homoseryl,
isoleucyl,
D-isoleucyl,
D-leucyl,
D-lysyl(N-epsilon-nicotinyl),
D-lysyl,
D-methionyl,
D-3-(4-methylphenyl)alanyl,
D-3-(naphth-1-yl)alanyl,
D-3-(naphth-2-yl)alanyl,
D-3-(4-nitrophenyl)alanyl,
D-norleucyl,
D-ornithyl,
D-penicillaminyl(S-acetamidomethyl),
D-penicillaminyl(S-benzyl),

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D-penicillaminy(S-methyl),
D-penicillaminy,
D-3-(pentafluorophenyl)alanyl,
D-phenylalanyl,
D-prolyl,
D-seryl(O-benzyl),
D-seryl,
D-(2-thienyl)alanyl,
D-threonyl(O-benzyl),
D-threonyl,
D-3-(3-trifluoromethylphenyl)alanyl,
D-(3,4,5-trifluorophenyl)alanyl,
D-tryptyl,
D-tyrosyl(O-ethyl),
D-tyrosyl, and
D-valyl;

Xaa₆ is an N-alkylated amino acid selected from the group consisting of N-(R³)-aspartyl, N-(R³)-glutamyl, N-(R³)-glycyl, N-(R³)-seryl, N-(R³)-threonyl, N-(R³)-threonyl(O-benzyl), and N-(R³)-tyrosyl, wherein R³ is as defined above; or Xaa₆ is an N-unalkylated amino acid selected from the group consisting of

alanyl,
allothreonyl,
D-allothreonyl,
allylglycyl,
asparaginyl,
aspartyl,
glutaminyl,
glycyl,
histidyl,
homoseryl,
D-homoseryl,
3-(4-hydroxymethylphenyl)alanyl,
isoleucyl,
lysyl(N-epsilon-acetyl),
methionyl,

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3-(naphth-2-yl)alanyl,
norvalyl,
octylglycyl,
prolyl,
3-(3-pyridyl)alanyl,
seryl,
D-seryl,
threonyl,
D-threonyl,
tryptyl,
tyrosyl, and
tyrosyl(O-methyl);

Xaa₇ is an N-alkylated amino acid selected from the group consisting of N-(R³)-alanyl, N-(R³)-glycyl, N-(R³)-isoleucyl, N-(R³)-leucyl, N-(R³)-D-leucyl, N-(R³)-norleucyl, N-(R³)-norvalyl, N-(R³)-seryl, N-(R³)-threonyl, and N-(R³)-valyl, wherein R³ is as defined above; or Xaa₇ is an N-unalkylated amino acid selected from the group consisting of

alanyl,
allothreonyl,
allylglycyl,
3-(4-amidophenyl)alanyl,
2-aminobutyryl,
arginyl,
asparaginyl,
cyclohexylalanyl,
glutaminyl,
D-glutaminyl,
glycyl,
homoalanyl,
homoseryl,
4-hydroxyprolyl,
leucyl,
D-leucyl,
lysyl(N-epsilon-acetyl),
methionyl sulfone,

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methionyl sulfoxide,
methionyl,
norleucyl,
norvalyl,
D-norvalyl,
octylglycyl,
ornithyl(N-delta-acetyl),
phenylalanyl,
propargylglycyl,
seryl,
D-seryl,
threonyl,
tryptyl,
tyrosyl, and
valyl;

Xaa₈ is an N-alkylated amino acid selected from the group consisting of N-(R³)-alanyl, N-(R³)-D-alanyl, N-(R³)-isoleucyl, and N-(R³)-leucyl, wherein R³ is as defined above; or Xaa₈ is an N-unalkylated amino acid selected from the group consisting of

alanyl,
alloisoleucyl,
D-alloisoleucyl,
allylglycyl,
citrullyl,
glycyl,
isoleucyl,
D-isoleucyl,
leucyl,
D-leucyl,
lysyl(N-epsilon-acetyl),
D-lysyl(N-epsilon-acetyl),
methionyl,
3-(naphth-1-yl)alanyl,
norvalyl,
prolyl,

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D-proyl, and
valyl;

Xaa₉ is the N-alkylated amino acid N-(R³)-arginyl, wherein R³ is as defined above; or Xaa₉ is an N-unalkylated amino acid selected from the group consisting of

[(4-amino-N-isopropyl)cyclohexyl]alanyl,
3-(4-amino-N-isopropylphenyl)alanyl,
arginyl(N^GN^{G'}diethyl),
arginyl,
D-arginyl,
citrullyl,
glutaminyl,
3-(4-guanidinophenyl)alanyl,
histidyl,
homoarginyl,
lysyl(N-epsilon-isopropyl),
lysyl(N-epsilon-nicotinyl),
lysyl,
norarginyl,
ornithyl,
ornithyl[N-delta-(2-imidazolinyl)],
ornithyl(N-delta-isopropyl), and
3-(3-pyridyl)alanyl;

Xaa₁₀ is an N-alkylated amino acid selected from the group consisting of N-(R³)-alanyl, N-(R³)-D-alanyl, N-(R³)-glycyl, N-(R³)-homoalanyl, and N-(R³)-norvalyl, wherein R³ is as defined above; or Xaa₁₀ is an N-unalkylated amino acid selected from the group consisting of

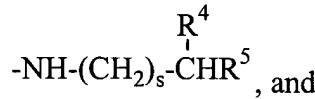
D-alanyl,
2-aminobutyryl,
D-2-aminobutyryl,
2-aminoisobutyryl,
3,4-dehydroprolyl,
4-hydroxyprolyl,
phenylalanyl,
prolyl,

D-prolyl,
1,2,3,4-tetrahydroisoquinoline-3-carbonyl, and
D-valyl; and

Xaa₁₁ is a hydroxy group or an amino acid amide selected from the group consisting of:

alanylamide,
D-alanyl amide,
alanylethylamide,
D-alanylethylamide,
azaglycylamide,
glycylamide,
glycylethylamide,
lysyl(N-epsilon-acetyl),
D-lysyl(N-epsilon-acetyl),
N-methyl-D-alanyl amide,
sarcosylamide,
seryl amide,
D-seryl amide,

a residue represented by the formula



a group represented by the formula -NH-R⁶; wherein

s is an integer from 0 to 8;

R⁴ is selected from the group consisting of hydrogen, alkyl, and a 5- to 6-membered cycloalkyl ring;

R⁵ is selected from the group consisting of hydrogen, alkoxy, alkyl, aryl, cycloalkenyl, cycloalkyl, heterocycle, and hydroxy;

provided that s is not zero when R⁵ is hydroxy or alkoxy; and

R⁶ is selected from hydrogen and hydroxy.